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(54) Germicidal Agents

(57) A germicidal agent of use e.g. for preserving industrial fluids, raw materials or products or for disinfecting a locus comprises in aqueous solution 0.1 to 5 parts by weight of 2-methyl-3-oxo-5-chlorothiazoline-1,2; 16 to 28.5 parts by weight of dimethylolurea and 40 to 72 parts by weight of one or more adduct formed between 2 mol formaldehyde and an aliphatic glycol with 2 to 8 C-atoms and/or a monoalkyl ether of such a glycol having 1 to 6 C-atoms in the ether radical. The agent may be made by combining an aqueous solution of the urea and the formaldehyde adduct with an aqueous solution of the thiazoline derivative.

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SPECIFICATION
Germicidal Agents

The invention relates to germicidal agents which can be used for example as preservative agents or disinfectants.

In the field of technology, many conditions make it both necessary and desirable to preserve liquids, emulsions or solid products. Substances and solutions of the most diverse chemical composition are subject to decomposition after a shorter or longer period of time by the action of germs such as bacteria, yeasts fungi, and the like, especially in the simultaneous presence of water.

A great number of compounds of very varied structure having bactericidal and/or fungicidal activity are employed as industrial preservative or disinfectant agents. The activity of a given germicidal compound is in most cases more or less pronounced against different types of germs, and combinations of different compounds are used frequently for this reason.

In addition to a widest possible activity spectrum against various bacteria and fungi, an industrial germicidal agent should also have a good solubility in water or polar solvents, pH-stability, thermal stability and a relatively high inertness to ionic compounds. To these criteria must be added the requirement that the agents do not have a high level of toxicity to warm-blooded species, and in particular do not lead to skin irritation among users. As the nature of these requirements will suggest, it is often very difficult to satisfy them all, precluding the use of a single substance in many cases.

Thus, the application of the known agents is often fraught with difficulties owing to their poor solubility, ionic or pH-sensitivity, and toxicity, to which must be added that owing to their mostly differing effectiveness against different germs, a long-lasting and comprehensive preserving effect cannot be achieved in most of the cases. Moreover, the most active compounds often show a relatively poor cutaneous tolerance, so that the working with such agents, such as formaldehyde-containing solutions for example, can lead to irritation of skin and of the mucous membranes and other health-damaging effects.

The fundamental purpose of the invention is the development of a novel germicidal agent suited for industrial application.

The present invention provides a germicidal agent comprising in aqueous solution 0.1 to 5 parts by weight of 2-methyl-3-oxo-5-chlorothiazoline-1,2, 16 to 28.5 parts by weight of dimethylolurea and 40 to 72 parts by weight of one or more adduct formed between 2 mol formaldehyde and an aliphatic glycol with 2 to 8 C-atoms and/or a monoalkyl ether of such a glycol having 1 to 6 C-atoms in the ether radical.

Whilst the germicidal activity of the individual compounds we employ is known *per se* the pronounced synergistic activity of the above-indicated combination constitutes a wholly surprising observation.

Adducts formed of 2 mol formaldehyde and aliphatic glycols and/or their monoalkyl ethers have already been in use as disinfectants or preservative agents for a long time. These compounds, which liberate formaldehyde only in strongly acid media, are considered to be substantially better tolerated than solutions of free formaldehyde and display a notable activity against bacteria and fungi. Dimethylolurea has also been known for a long time and is used as a weak disinfectant in spite of its relatively low bactericidal and fungicidal effect.

2-methyl-3-oxo-5-chlorothiazoline-1,2, otherwise 5-chloro-2-methyl-3-oxo-1,2-thiazoline, has been made commercially available in recent years by the firm Roehm and Haas, of Philadelphia, under the Trade Name of "Kathon 886" and recommended for use as an effective bactericidal compound. The aqueous solution marketed under the Trade Name "Kathon 886" contains approximately 14% of a mixture consisting of 2-methyl-3-oxo-5-chlorothiazoline-1,2, and the unchlorinated parent compound, that is, 2-methyl-3-oxothiazoline-1,2, in which the chlorinated compound predominates to a large extent. This aqueous solution further contains one mol of magnesium chloride and 1 mol magnesium nitrate as stabiliser, per mol of heterocyclic parent compound present before chlorination.

However, in aqueous solution and even in a very highly diluted state, 2-methyl-3-oxo-5-chloro-thiazoline-1,2 is so aggresive that owing to its highly damaging effects on the skin it has found but little practical use. Even a single drop of the highly dilute solution is enough to cause blistering of the skin and long-lasting, painful skin irritation.

It has now been unexpectedly found, that agents according to the invention and containing specified amounts of the specified compounds have a notable synergistic effectiveness. The synergistic effectiveness is shown clearly by the substantially increased bactericidal and fungicidal activity relative to the components considered in isolation. Moreover, the local tolerance to the agent is improved to such an extent that surprisingly we find little skin irritation occurs when working with the solution even with prolonged contact and despite the presence of the highly aggresive 2-methyl-3-oxo-5-chloro-thiazoline-1,2.

The present germicidal agents can be prepared by mixing 80 to 95 parts of an aque us solution of a mixtur consisting of 20 to 30% dimethylolurea and 50 to 75% of one or more adducts formed between 2 mol formaldehyde and an aliphatic glycol with 2 to 8 C-atoms and/or a monoalkyl ether of such a glycol having 1 to 6 C-atoms in the ether radical with 20 to 5 parts of an aqueous solution of 2-

methyl-3-oxo-5-chlorothiazoline-1,2 of concentration such that the resultant mixture contains 0.1 to 5% of 2-methyl-3-oxo-5-chlorothiazoline-1,2.

Preservative agents according to the invention can be employed in numerous industrial fields. The product has proved particularly successful in trials on the pre- and post-treatment of metal-working liquids, and grinding and drilling oil emulsions. In these applications, the agent is used mostly at concentrations of 0.01—0.3%. We find that antimicrobial activity is independent of the pH-value, and moreover is not influenced by anionic, cationic or nonionic components; an excellent preservation should thus be possible even with very small additions.

For the treatment of industrial recycle waters against micro-organisms and algae, the agents according to the invention are typically employed at concentrations of 0.03—0.05%. Furthermore, they can be used in the long-term preservation of wax emulsions, dispersion dyestuffs, adhesives, glues, emulsifiers, synthetic wetting agents, dispersions and suspensions, typically at a concentration of the order of 0.02—0.1%. For raw materials of the chemical industry, for example glues, white glues, adhesives, water-soluble dyes and hydraulic fluids a working concentration of 0.05—0.2% is recommended.

A further field of application is the use as a bactericidal agent for industrial disinfectant cleansing agents of all types as well as in polishing waxes. Depending on the desired disinfectant effect, the proportion of the agent according to the invention in the application solution usually amounts to a concentration of the order of 0.02—1.0%. When used as a bactericidal agent in disinfectant, non-dilutable floor-maintenance agents for the so-called bactericidal impregnation, a somewhat higher concentration of about 0.5—2.0% will preferably be applied.

A further important field of application is in the use as slime-suppressing agent in paper and cellulose manufacture, against aerobic and anaerobic bacteria, fungi, yeasts as well as specific slime producers. By the addition of about 25—250 ppm of an agent according to the invention to the stock suspension, slime formation can be reliably prevented which otherwise could lead to paperbreak on the cylinder (and must therefore be avoided under any circumstances).

The invention will be illustrated with reference to the following Examples:

Example 1

Preparation of a Preservative and Disinfecting Agent

9.2 kg of a solution in water of 2.7 kg of dimethylolurea and 5.5 kg of the addition product formed between ethylene glycol and 2 mol formaldehyde was mixed with 0.8 kg of a commercially available aqueous 14% strength solution of 2-methyl-3-oxo-5-chlorothiazoline-1,2. The resulting solution thus comprised about 1.1% 2-methyl-3-oxo-5-chlorothiazoline-1,2 and 92% of a mixture consisting of 27% dimethylolurea and 65% of an adduct formed of 2 mol formaldehyde and ethylene glycol.

The odour of the finished solutions was mild and neutral. However, the odour of the mixture can be varied if desired e.g. by the addition of a small quantity of a commercially available fragrance mixture.

Example 2

Testing of Local and Systemic Tolerance

For testing the local tolerance, the agent of Example 1 was tested on rabbit skin. The experimental animals employed were male and female NZW-rabbits, with a body weight between 2.3 and 2.8 kg.

The rabbits were divided into 6 groups of approximately equal body weight and treated in the following manner:

The area for application of the test substance was sheared in an injury-free manner with a manual shearing machine 3 days prior to treatment and thereafter every three days during the long-term observation period. The skin thus exposed was about 2.5x2.5 cm in size and located between the fore and rear extremities on the backs of the animals.

For half of the animals, the application was made on the intact skin, in the other half the area of application was scarified. 0.5 ml of the test substance was first of all applied to a piece of linen cloth measuring 2.5x2.5 cm, covered with a plastic foil of equal size and fastened to the back of the animals with a gummed bandage. The cloth was left on the skin for 24 hours.

In each experimental group consisting of 6 animals, 3 male and 3 female animals with intact and scarified skin respectively were treated. The first group received an undiluted solution of the agent according to the invention, the second group was treated with a 50% aqu ous soluti n of the agent according to the invention, the third group with a 25% solution and the fifth group with a 6.25% solution, whilst the sixth group as control group received only distilled water.

The cutaneous reaction was evaluated at the end of the exposure period, as well as 48, 72, 96, 120, 144 and 168 hours thereafter.

The single application of the undiluted agent according to the invention to the intact and scarified dorsal skin of rabbits led to erythema formation. It appeared already immediately at the end of the 24-

hours exposure period, remained observable for a further 120 hours thereafter and then began to decrease. The skin condition was normal again after 168 hours at the latest.

The 50, 25, and 12.5% concentration of the agent each provoked a slight reddening, which disappeared completely after 144 hours. The highest concentration tolerated without reaction in these experiments was 6.25% of the preservative agent. Oedema formation was not observed in any of the experiments. More far-reaching skin changes such as rhagadea or necrosis were not found. The hair growth rate was normal.

No indications of systemic intolerance could be observed in any of the experimental groups. The behaviour, general condition, fodder and drinking-water intake and development of body weight did not show any abnormalities.

Example 3

Germicidal Activity in Suspension Tests

In accordance with conventional procedures the germicidal activity of the germicidal agent embodying the invention was evaluated and gave the following results:

Test organism	*%*	*4 hrs*	*1 day*	*2 days*	*3 days*
Yeast, type 28b	0.01	+	+	(+)	(+)
	0.02	+	(+)	—	—
	0.03	+	—	—	—
	0.05	+	—	—	—
	0.075	(+)	—	—	—
	0.1	(+)	—	—	—
Pseudomonas	0.01	+	(+)	(+)	(+)
	0.02	+	—	—	—
	0.03	+	—	—	—
	0.05	+	—	—	—
	0.075	(+)	—	—	—
	0.1	(+)	—	—	—
Aspergillus	0.01		+	+	(+)
	0.02		+	(+)	—
	0.03		—	—	—
	0.05		—	—	—
	0.075		—	—	—
	0.1		—	—	—
Mucor	0.01		+	+	—
	0.02		+	+	—
	0.03		—	—	—
	0.05		—	—	—
	0.075		—	—	—
	0.1		—	—	—

—=Test organism destroyed
+=Growth, no destruction
(+)=Isolated colonies

Claims

1. A germicidal agent comprising in aqueous solution 0.1 to 5 parts by weight of 2-methyl-3-oxo-5-chlorothiazoline-1,2, 16 to 28.5 parts by weight of dimethylolurea and 40 to 72 parts by weight of one or more adduct formed between 2 mol formaldehyde and an aliphatic glycol with 2 to 8 C-atoms and/or a monoalkyl ether of such a glycol having 1 to 6 C-atoms in the ether radical.

2. An agent acc rding to Claim 1 comprising about 1.1% 2-methyl-3-oxo-5-chlorothiazoline-1,2 and about 92% of a mixture c nsisting of ab ut 27% dimethylolurea and about 65% of an adduct formed of 2 mol formaldehyde and ethylene glycol.

3. An agent according to Claim 1 or 2 which contains a small quantity of 2-methyl-3-oxothiazoline-1,2.

4. A method of manufacturing a germicidal agent which comprises mixing 80 to 95% parts of an aqueous solution of a mixture consisting of 20 to 30% dimethylolurea and 50 to 75% of one or m re adducts formed between 2 mol formaldehyde and an aliphatic glycol with 2 t 8 C-atoms and/or a monoalkyl ether of such a glycol having 1 to 6 C-atoms in the ether radical with 20 to 5 parts of an

aqueous solution of 2-methyl-3-oxo-5-chlorothiazoline-1,2 of concentration such that the resultant mixture contains 0.1 to 5% of 2-methyl-3-oxo-5-chlorothiazoline-1,2.

5. A process for preserving a liquid, emulsion or solid which comprises incorporating a germicidal agent according to any of Claims 1 t 3 or incorporating a g rmicidal agent produced by a method according to Claim 4.

6. A process for disinfecting a locus which comprises applying a germicidal agent according to any of Claims 1 to 3 or applying a germicidal agent produced by a method according to Claim 4.

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